Notice of Allowability	Application No.	Applicant(s)	
	08/852,020	MARUYAMA ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the papers filed 7/12/2004*.

2. ☒ The allowed claim(s) is/are *57-60*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☒ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☒ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☒ hereto or 2) ☒ to Paper No./Mail Date *12/23/1997*.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 7-20-2000
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

GERRY LEFFERS
PRIMARY EXAMINER

EXAMINER'S AMENDMENT

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/12/2004 has been entered.

An examiner's amendment to the record appears below. The amendments to the claims are made to limit the recited vectors and phage to those embodiments where the anchor matrix protein expressed on the phage particle as part of a fusion protein is the D protein of lambdoid phage. The specification is amended in the Brief Description of the Drawings to insert appropriate SEQ ID NOS and to correct a typographical error where phage λ is mislabeled (i.e. as phage "γ"). Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Thomas Fitting on 9/28/2004. The application has been amended as follows:

In the claims:

Claim 57. (currently amended) A recombinant lambdoid bacteriophage vector comprising a nucleotide sequence that (i) defines the lambdoid elements for replication and packaging of the vector into an assembled bacteriophage, and (ii) encodes a conditionally

suppressible cistron for expression of a [matrix anchor] lambdoid bacteriophage head protein and a fusion protein that comprises:

a) a promoter for transcribing the cistron,

b) a first upstream translatable sequence that encodes a pD lambdoid bacteriophage head [or tail] protein,

c) a first ribosome binding site to initiate translation of said upstream translatable sequence,

d) a second translatable sequence operatively linked downstream to said first translatable sequence that (i) encodes a linker polypeptide in frame with said head [or tail] protein and (ii) includes a sequence adapted for ligation of an insert polynucleotide that defines a third translatable sequence downstream from said second translatable sequence that encodes a preselected polypeptide, and

e) a suppressor termination codon within said second translatable sequence that upon suppression results in read-through to form a fusion polypeptide consisting of said [matrix anchor] pD lambdoid bacteriophage head protein, linker polypeptide and preselected polypeptide.

Claim 58. (previously presented) The vector of claim 57 wherein said second translatable sequence further includes a nucleotide sequence that defines a second ribosome binding site to initiate translation of said third translatable sequence.

Claim 59. (currently amended) A recombinant lambdoid bacteriophage comprising a matrix of proteins encapsulating a lambdoid genome encoding a fusion protein, said matrix including said fusion protein, surface accessible in said matrix, and said fusion protein consists of, in the direction of amino terminus to carboxy terminus, a pD lambdoid bacteriophage head [or tail] protein, a linker polypeptide and a preselected polypeptide.

Claim 60. (previously presented) The lambdoid bacteriophage of claim 59 wherein said preselected polypeptide defines a biologically active protein selected from the group consisting of an enzyme, a ligand and a receptor.

In the specification:

At page 6, line 20 through page 8, line 32, the following changes have been made to the Brief Description of the Drawings (deleted sections are indicated by brackets ([]), and inserted elements are in **bold**):

[Figure 1] **Figure 1** illustrates a flow chart of the construction of the [γV' sac] **λV' sac** vector. Also indicated is the partial nucleotide and amino acid sequence of the [γV' sac] **λV' sac** vector. The amino acid sequence is given in SEQ ID NO: 9. The top strand of the nucleotide sequence form left to right is given in SEQ ID NO: 10. The bottom strand of the nucleotide sequence from left to right is given in SEQ ID NO: 11. The left arm of [γ] λ phage is depicted with genes Nu1 through J shown as boxes. The arrow at the top of the figure indicates the number of kilobase pairs (kb) of the [γ] λ vector. The DNA segment from nucleotide 5505 to 10,325 and encoding genes Nu3 through G was removed from the [γ] λ vector by digestion with

the enzymes BamHI and NsiI. This fragment is shown as a line with nucleotide numbers below the topmost [γ] λ genetic map. Insertion of the DNA fragment into the M13mp19 and pUC12 vectors, site-directed mutagenesis to introduce the amber stop codon and Sac I restriction site, and subsequent combination with the [[γ2000] **λ2000** vector to create the [γV' sac] **λV' sac** vector are as described in Example 1a1[)]. A portion of the resulting [γV' sac] **λV' sac** vector is shown at the bottom of the figure consisting of the amino acid and nucleotide sequence of part of the mutagenized [V] **V** gene. The nucleotide positions which were mutagenized are underlined and a newly created Sac I site is indicated in boldface type. The amber suppressor stop codon is indicated by the nucleotide sequence TAG which is underlined. Numbers at the left side from top to bottom indicate the amino acid number of the [pV] **pV** gene and the nucleotide sequence from the left arm of [γ] λ, respectively. Abbreviations used to indicate the corresponding restriction sites are: Ba, BamHI; Bc, BclI; Aa, AatII; Ap, ApaI; N, NsiI; E, EcoRI; and ApL, ApaLI.

[Figure 2] **Figure 2** illustrates partial sequence of the [γblue and γfoo] **λblue and λfoo** vectors. The partial sequences illustrate the amino acid and nucleotide sequence between the amber stop codon of the [pV] **pV** protein, indicated by TAG and underlined, and the downstream restriction sites. The names of the restriction sites are indicated below the sites and the nucleotide sequences defining the restriction sites are underlined. The **corresponding** amino acid sequence is given above the nucleotide sequence **for each of λV'mcs,** [γblue and γfoo] **λblue and λfoo**. **The λV'mcs amino acid and nucleotide sequences are given as SEQ ID NO: 12 and SEQ ID NO: 13, respectively.** The [γblue] **λblue** amino acid and nucleotide sequences are given as [SEQ ID NOs 14 and 15] **SEQ ID NO: 14 and SEQ ID NO: 15,**

respectively. The [γfoo] **λfoo** amino acid and nucleotide sequences are given from amino acid residues 178 to 237 of SEQ ID NO: 6 and base number 547 to 726 of SEQ ID NO: 5, respectively. The amino acid sequence downstream of the suppressor codon is expressed at the carboxy terminus of [pV] **pV** in the presence of a suppressor tRNA as described in Example 1a2. Numbers in the right-hand column, from top to bottom, indicate the amino acid position from the start codon of the [pV] **pV** gene and the nucleotide sequence of the [γ] λ vector, from the beginning of the left arm, at the end of the respective lines.

The Pro-Thr linker sequence in the [γfoo] **λfoo** vector (from base number 562 to 624 and amino acid residue sequence from 183 to 203 of SEQ ID NO: 5) is directly downstream of the SfiI restriction site. The DNA expression control sequence for expressing translatable DNA inserted into any of the downstream restriction sites are included in the linker sequence. The Pribnow box, CAGGAA, is double underlined and is 6 nucleotides upstream of the start codon, methionine (M). The second amino acid, threonine (T) is underlined.

[Figure 3] **Figure 3** illustrates the detection of [γ] λ phage proteins by gel electrophoresis and Western blotting. Purified phage proteins were detected on a polyacrylamide gel by staining with PAGE blue 84 (BDH) (lanes A, B, and C on the left side) and by reactivity with mouse anti-B-gal antibody (lanes A, B and C on the right side) as described in Example 2a4). Lane A is [γfoo] **λfoo** phage proteins when grown on MC8 (su^+); lane B is [γgal] **λB-gal** phage proteins when grown on EQ166 (su^-); and lane C is [γB-gal] **λB-gal** phage proteins when grown on MC8 (su^+). Molecular weight standards (GIBCO/BRL) (unlabeled lane in the center) are myosin heavy chain (200 kDa), phosphorylase b (97.4 kDa), and bovine serum albumin (68 kDa).

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: upon further review of the prior art and in view of the teachings of Mikawa et al, applicants' arguments are persuasive with regard to embodiments that are limited to the lambdoid bacteriophage head protein pD. Applicants have agreed to limit the instant claims to pD fusions. In particular, it was known in the art at the time of the invention that the D protein was not essential for assembly of mature capsids under all conditions and that it might be suitable for manipulation for phage display (e.g. Sternberg et al, Proc. Natl. Acad. Sci. USA, Vol. 92, pages 1609-1613, 1995; see especially page 1609, first column and references 5-7). Further, applicants' argument that the phage vectors exemplified by Mikawa et al are evidence that the instant application was enabling for protein D fusions is persuasive (J. Mol. Biol., Vol. 262, pages 21-30, 1996; e.g. see pages 26-27, Figures 4-5). Considering the state of the art and the disclosure of the instant specification, it would not have required undue, unpredictable experimentation to obtain the vectors taught by Mikawa et al.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Drawings

The drawings filed on 5/6/1997 are acceptable subject to correction of the informalities indicated on the attached "Notice of Draftsperson's Patent Drawing Review," PTO-948 (originally mailed in the office action of 12/23/1997). In order to avoid abandonment of this application, correction is required in reply to the Office action. The correction will not be held in abeyance.

Conclusion

Claims 57-60 are allowed (now claims 1-4).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

ggl

GERRY LEFFERS
PRIMARY EXAMINER